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(71) Applicant (for DE only): **PHILIPS INTELLECTUAL PROPERTY & STANDARDS GMBH [DE/DE]**; Stein-damm 94, 20099 Hamburg (DE).

(71) Applicant (for all designated States except DE, US): **KONINKLIJKE PHILIPS ELECTRONICS N.V. [NL/NL]**; Groenewoudseweg 1, NL-5621 BA Eindhoven (NL).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **GLEICH, Bernhard [DE/DE]**; c/o Philips Intellectual Property & Standards GmbH, Weisshausstr. 2, 52066 Aachen (DE).

(74) Agent: **MEYER, Michael**; Philips Intellectual Property & Standards GmbH, Weisshausstr. 2, 52066 Aachen (DE).

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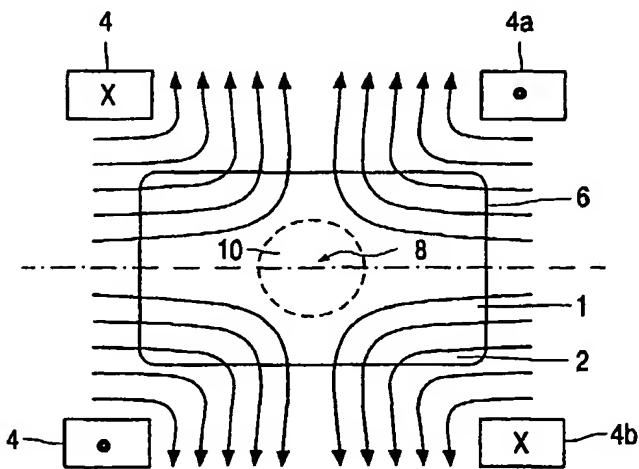
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[Continued on next page]

(54) Title: **METHOD OF DETERMINING STATE VARIABLES AND CHANGES IN STATE VARIABLES**



WO 2004/091397 A3

change, and e) evaluating the signals so as to obtain information about the change in the spatial distribution of the magnetic particles and/or physical, chemical and/or biological state variables or the change therein in the examination area. The invention further relates to magnetic particle compositions and their use in a method according to the invention. The invention further also relates to an apparatus for the measurement of state variables.

(57) Abstract: The present invention relates to a method of determining physical, chemical and/or biological state variables, particularly substance concentrations, temperature, pH and/or physical fields, and/or the change in these state variables in an examination area of an examination object by determining the change in the spatial distribution of magnetic particles in this examination area by means of the following steps: a) introducing magnetic particles into at least part of the examination area in a first state in which at least some of the magnetic particles are agglomerated and/or coupled to one another in pairs or more, or introducing magnetic particles in a second state in which the particles are deagglomerated and/or decoupled, b) generating a magnetic field with a first part-area having a low magnetic field strength and a second part-area having a higher magnetic field strength, c) changing the spatial position on the two part-areas in the examination area or changing the magnetic field strength in the first part-area, d) detecting signals that depend on the magnetization in the examination area that is influenced by this



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(15) Information about Correction:

see PCT Gazette No. 12/2005 of 24 March 2005, Section II

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/050449

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/06 A61K49/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 095 124 A (BRUKER MEDIZINTECH) 30 November 1983 (1983-11-30) cited in the application claims 1-3	40
A	US 4 136 683 A (GORDON ROBERT T) 30 January 1979 (1979-01-30) the whole document	40
A	US 6 082 366 A (ANDRAE WILFRIED ET AL) 4 July 2000 (2000-07-04) column 4, line 48 - column 5, line 55	40
P,A	EP 1 304 542 A (PHILIPS CORP INTELLECTUAL PTY ; KONINKL PHILIPS ELECTRONICS NV (NL)) 23 April 2003 (2003-04-23) paragraphs [0030] - [0040], [0050] - [0054]	40

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL -2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Lohmann, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/050449

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-20, 31, 39
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-20, 40

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20, 40

A method and an apparatus for determining physical, chemical and/or biological properties or state variables in an examination area by determining the spatial distribution of magnetic particles in this area and use of monodomain particles.

2. claims: 21-31

Magnetic gas bubble composition comprising gas bubbles, magnetic gas bubble precursor for its manufacture and use as an imaging agent, in particular with acoustic waves.

3. claims: 32-37

(Kit of) magnetic particle compositions wherein the magnetic particles are bound to functional binding units or are agglomerated/coupled together and have a particular average particle to particle distance.

4. claims: 38, 39

Magnetic particle composition having a particular magnetization curve and its use.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-20, 31, 39

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/IB2004/050449

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0095124	A 30-11-1983	DE 3219832 A1 AU 551305 B2 AU 1490083 A EP 0095124 A1 JP 58218950 A ZA 8303784 A		01-12-1983 24-04-1986 01-12-1983 30-11-1983 20-12-1983 28-03-1984
US 4136683	A 30-01-1979	NONE		
US 6082366	A 04-07-2000	DE 19532676 C1 CN 1195404 A DE 19707556 C1 WO 9709640 A1 EP 0848832 A1 ES 2175126 T3 JP 11512007 T		07-05-1997 07-10-1998 09-07-1998 13-03-1997 24-06-1998 16-11-2002 19-10-1999
EP 1304542	A 23-04-2003	DE 10151778 A1 CN 1412550 A EP 1304542 A2 JP 2003199767 A US 2003085703 A1		08-05-2003 23-04-2003 23-04-2003 15-07-2003 08-05-2003